Claims

We claim:

1. A method of identifying small molecules that affect a biological event of interest, the method comprising the steps of:

providing a collection of small molecules, each of which is attached to a solid support, which solid support is associated with a molecular sensor characterized in that at least one spectroscopic property of the sensor is altered in the presence of nitric oxide;

providing cells containing a reporter gene that encodes a nitric oxide synthase, expression of the reporter gene being indicative of occurrence or non-occurrence of a selected biological event involving the cells;

contacting the cells with the collection of small molecules; and

identifying solid supports with chemical sensors whose at least one spectroscopic property has become altered, the alteration in spectroscopic property revealing nitric oxide production, the production of nitric oxide revealing expression of the reporter gene, the reporter gene expression revealing occurrence or non-occurrence of the selected biological event, so that compounds attached or were attached to the identified solid support are revealed to have affected the biological event.

2. A method of identifying a test compound that affects a biological event of interest, the method comprising steps of:

providing a plurality of test compounds;

providing cells containing an inducible reporter gene, wherein expression of the reporter gene results in the production of a reporter gene product,

wherein the product is secreted by the cell,

wherein the product is detectable, and

wherein the presence of the products indicates occurrence or non-occurrence of a selected biological event;

contacting the cells with the plurality of test compounds; and

identifying test compounds which promote or inhibit a biological event based on production of the reporter gene product.

3. The method of claim 2, wherein the plurality of test compounds are attached to a solid support through a cleavable linkage.

4. The method of claim 2, wherein the linkage is severable by irradiation with light.

5. The method of claim 3, wherein the solid support is associated with a molecular sensor.

6. The method of claim 5, wherein the solid support is associated with a molecular sensor that can detect nitric oxide.

7. The method of claim 5, wherein the molecular sensor is 2,3-diaminonapthalene (DAN).

8. The method of claim 5, wherein the molecular sensor is diaminofluorescein.

9. The method of claim 4, wherein the molecular sensor is characterized in that at least one optical property of the sensor is altered in the presence of nitric oxide.

10. The method of claim 2, wherein the test compounds are small molecules.

11. The method of claim 2, wherein the plurality of test compounds is a combinatorial library of chemical compounds.

12. The method of claim 2, wherein the plurality of test compounds is a combinatorial library of small molecules.

13. The method of claim 2, wherein the test compounds are proteins.

14. The method of claim 2, wherein the test compounds are peptides.

15. The method of claim 2, wherein the test compounds are nucleic acids.

16. The method of claim 2, wherein the reporter gene encodes a reporter gene product that catalyzes the production of a chemical compound that is secreted by the cell.

17. The method of claim 2, wherein the reporter gene encodes a reporter gene product that is a small molecule.

18. The method of claim 2, wherein the reporter gene encodes a reporter gene product that catalyzes the production of a membrane permeable chemical compound that is detectable.

19. The method of claim 18, wherein the chemical compound is a gas at room temperature and 1 atm of pressure.

20. The method of claim 19, wherein the chemical compound is nitric oxide.

21. The method of claim 19, wherein the chemical compound is molecular oxygen.

22. The method of claim 19, wherein the chemical compound is carbon monoxide.

23. The method of claim 19, wherein the chemical compound is molecular nitrogen.

24. The method of claim 19, wherein the chemical compound is carbon dioxide.

25. The method of claim 2, wherein the cells are macrophages.

26. The method of claim 2, wherein the cells are yeast.

27. The method of claim 2, wherein the cells are mammalian cells.

28. The method of claim 2, wherein the cells are human cells.

29. The method of claim 2, wherein the cells are bacterial cells.

30. The method of claim 2, wherein the reporter gene is nitric oxide synthase.

31. The method of claim 2, wherein the reporter gene product is nitric oxide.

32. The method of claim 3, wherein the step of identifying comprises sorting the solid supports using fluorescence-activated bead sorting (FABS).

33. The method of claim 3, wherein the step of identifying comprises decoding tags on the solid support which correspond to the synthetic history of the test compound attached or was once attached to the bead or structural features of the test compound.

34. A library of test compounds attached to a solid support, wherein a chemical sensor is attached to the solid support.

35. The library of claim 34, wherein the chemical sensor is characterized in that at least one optical property of the sensor is altered in the presence of nitric oxide.

36. A method of synthesizing a combinatorial library, the method comprising steps of:

synthesizing a library of small molecules on a solid support by combinatorial chemistry methods;

attaching tags to the solid support which encode the synthesis or structural element; and

attaching a molecular sensor to the solid support able to detect the reporter gene product.

37. A method of providing a molecular sensor, the method comprising steps of:

providing a collection of chemical compounds linked to a solid support; and

attaching a molecular sensor to the solid support.

38. An assay system comprising a nitric oxide synthase gene, wherein the gene is a reporter gene.

39. An assay system comprising a nitric oxide synthase gene, wherein the gene is a reporter gene, and a molecular sensor capable of detecting nitric oxide.

40. An assay system comprising

a first construct encoding a DNA binding domain fused to a first protein of interest;

a second construct encoding an activation domain fused to a second protein of interest; and

a third construct comprising a binding site of the DNA binding domain functionally lined to a reporter gene.

41. The assay system of claim 40, wherein the DNA binding domain is LexA.

42. The assay system of claim 40, wherein the activation domain is B42.

43. The assay system of claim 40, wherein the reporter gene is nitric oxide synthase.

44. The assay system of claim 40, wherein the reporter gene is protein inhibitor of nitric oxide synthase (PIN).

45. The assay system of claim 40, wherein the first or second protein of interest is MDM2.

46. The assay system of claim 40, wherein the first or second protein of interest is p53.

47. A method of synthesizing and assaying a library of small molecules, the method comprising steps of:

synthesizing a library of small molecules on a solid support by combinatorial chemistry;

encoding a synthesis with an encoding tag attached to the solid support;

attaching a molecular sensor to the solid support wherein at least one spectroscopic property of said sensor is altered by chemical reactions involving nitric oxide;

providing cells containing a DNA sequence encoding a nitric oxide synthase wherein a protein-protein interaction of interest affects transcriptional activation of said sequence;

contacting cells with the solid supports containing the library, the encoding tag, and the sensor, wherein each cell is exposed to no more than one solid support;

releasing the small molecules from the solid supports;

contacting the cell with the small molecule;

allowing the small molecule to affect the protein-protein interaction;

allowing transcriptional activation of the DNA encoding a nitric oxide synthase;

allowing production of nitric oxide by a nitric oxide synthase;

allowing chemical reactions involving nitric oxide to alter at least one spectroscopic property of the sensor;

identifying solid supports with sensors having an altered spectroscopic property; and

decoding the encoding tag of sensors having an altered spectroscopic property to identify the small molecule affecting a protein-protein interaction of interest.